Contact Details Name: **Hospital** **Telephone:**

This protocol has 5 pages

PROPIONIC ACIDAEMIA –ACUTE DECOMPENSATION

(standard version)

- **Please read carefully. Meticulous treatment is very important as there is a high risk of neurological complications including cerebral oedema.**

- **If the instructions do not make sense or a problem is not addressed you must discuss your concerns with the consultant on call.**

1. Background

Propionic acidaemia is caused by a deficiency on propionyl CoA carboxylase, an enzyme on the catabolic pathway of aminoacids (isoleucine, valine, threonine and methionine) as well as cholesterol side chains, odd chain fatty acids and free propionate from the gut. Treatment is aimed at reducing the sources of the precursors so the patients are treated with a low protein diet and medicines - carnitine and metronidazole.

Decompensation is often triggered by metabolic stress such as febrile illness, particularly diarrhoea or vomiting, fasting, or constipation, but an obvious cause is not always apparent. The early signs of decompensation may be subtle, lethargy, even worse appetite than usual or exacerbation of pre-exiting neurological signs (movement disorder, etc). Vomiting is common and should always be taken seriously. However the signs may be difficult to assess such as irritability or just 'not right'. Always listen to parents carefully as they probably know much more than you do.

2. Admission

Almost all patients who present to hospital will require admission. Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child does not improve.

- **If there is any doubt at all, the child must be admitted, even if only necessary for a short period of observation.**

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3. Initial plan and management in hospital

⇨ If the child is shocked or clearly very ill arrange for admission to ITU/High dependency unit.

⇨ If admitted to metabolic/general ward make a careful clinical assessment including blood pressure and even if the patient does not appear encephalopathic enter a Glasgow coma score (for details click here). This is very important since should the child deteriorate particularly around the time of a change of shifts, the new team will recognise any change.

The following tests should be done:

BLOOD:	pH and gases
	Ammonia, Lactate
	Glucose (laboratory and bedside strip test)
	Urea & Electrolytes, Calcium, Phosphate and ALP
	Full blood count
	Amylase/lipase *(if pancreatitis a possibility)*
	Blood spot acylcarnitines
	Blood culture
URINE TESTS	ketones

Complications

There are many complications of the disorders but some are particularly problematic.

1. Pancreatitis. This is probably considerably more common than recognised, partly because it is not easy to diagnose with confidence. It should be suspected if there is abdominal pain, shock out of proportion to other symptoms or hypocalcaemia. Plasma lipase and amylase activity may not be raised, particularly at an early stage. Abdominal ultrasound may be helpful.

2. Cardiomyopathy and cardiac arrhythmias. Cardiomyopathy may develop at any time but for reasons not well understood may occur during recovery phase. Arrange echocardiography if there are signs of cardio-respiratory problems. Cardiac arrhythmias, notably long Q-T, are an important complication that may be responsible for sudden death. These may vary from time to time so all sick patients should be on a monitor.

3. Stroke-like episodes. These may occur at any time, frequently of sudden onset and when appearing to recover. They often involve the basal ganglia and present as a movement disorder.

For more information about the complications please click here

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4. Management

Management decisions should be based primarily on the **clinical** status. The first decision about therapy is whether the child can be treated orally or will need intravenous therapy.

- Factors that will influence the decision include, how ill is the child and have they deteriorated suddenly in the past?
- Can the child tolerate oral fluids?

If the child is relatively well - may be treated orally but assess very carefully.
If the child is obviously unwell - must be treated with intravenous fluids

If there is any doubt at all, put up an intravenous line.

A. ORAL.

If the child is relatively well and not vomiting oral feeds may be given.
The emergency regimen should be used. This may be given as regular frequent drinks but if the patient is at risk of vomiting or is nauseated fluid should be given either continuously or as small boluses more frequently. For more information about the emergency oral management click here

Age (years)	Glucose polymer concentration (g/100ml)*	Total daily volume**
0-1	10	150-200 ml/kg
1-2	15	100 ml/kg
2-6	20	1200-1500 ml
6-10	20	1500-2000 ml
>10	25	2000 ml

* If necessary, seek help from your local dietitian. In an emergency a heaped 5 ml medicine spoon holds approximately 7g of glucose polymer.

**For each drink the volume will generally be this figure divided by 12 and given 2 hourly but if the patient is nauseated or refuses try frequent smaller drinks or a continuous naso-gastric infusion.

Electrolytes should be added to the drinks using standard rehydration mixtures following manufacturer's instructions but substituting glucose polymer solution for water.

Medicines

- Carnitine 100 – 200mg mg/kg in 4 divided doses
- Metronidazole 7.5 mg/kg per dose 8 hourly
- Treat any infection
- Treat constipation (which increases propionate absorption from the gut. Do **not** use lactulose as this can be fermented to propionate by gut bacteria)

B. INTRAVENOUS.

If the child is unwell

- Give Glucose 200 mg/kg **at once** (2 ml/kg of 10% glucose or 1ml/kg of 20% glucose) over a few minutes.
- Give normal saline 10 ml/kg as a bolus immediately after the glucose unless the peripheral circulation is poor or the patient is frankly shocked, give 20 ml/kg normal saline instead of the 10 ml/kg.. Repeat the saline bolus if the poor circulation persists as for a shocked non-metabolic patient..
- Continue with glucose 10% at 5 ml/kg/h until next solution ready. – see below

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- Quickly calculate the deficit and maintenance and prepare the intravenous fluids
  - Deficit: estimate from clinical signs if no recent weight available
  - Maintenance: Formula for calculating daily maintenance fluid volume (BNF for children) 100ml/kg for 1st 10kg then 50 ml/kg for next 10kg then 20ml/kg thereafter, using calculated rehydrated weight. Deduct the fluid already given from the total for the first 24 hours.
  - Give 0.45% saline/10% glucose (for instructions to make this solution click here).

- Having calculated the deficit and the maintenance, give 1/3 of the total for 24 hours over the next 6 hours and the remainder in 18 hours. If intravenous fluids are still needed, continue with the same solution.
- Recheck the electrolytes every 24 hours if still on IV fluids.

- Hyperglycaemia can be a problem. If the blood glucose exceeds the 8 mmol/l, start an insulin infusion using the local diabetic protocol rather than reducing the glucose intake. **Strict supervision is essential.**

- Potassium can be added, if appropriate, once urine flow is normal and the plasma potassium concentration is known.

4.2 Acidosis

- WARNING severe acidosis (pH <7.2 or base deficit > 10 mmol/l) is potentially very dangerous. Patients who have a respiratory (or cardiac) arrest are usually difficult to resuscitate. **Always** consider elective assisted ventilation

Sodium bicarbonate is not given routinely but if acidosis persists after correction of perfusion, sodium bicarbonate may be needed if the pH <7.2 or the pH is deteriorating rapidly or the base deficit is greater than 10 mmol/l.

Initially give a half correction [0.15 x weight x base deficit (mmol/l)] mmol sodium bicarbonate over at least 30 minutes. 1 ml of sodium bicarbonate 8.4% contains 1 mmol but this solution should be diluted *at least* 1ml to 5ml of 5% glucose. Then review and check U&E and pH & blood gases. The acidosis normally corrects fairly quickly so that repeat doses of sodium bicarbonate should only occasionally be needed. If further doses of sodium bicarbonate appear to be needed, discuss with the consultant. Before doing so ask why? Is perfusion normal? What is the blood pressure, capillary refill time and urine flow? Could the patient have pancreatitis or cardiomyopathy? The treatment that will need to be considered is haemofiltration (possibly haemodialysis), assisted ventilation and inotropes. Such treatment should be under specialist metabolic supervision.

- Intra-lipid may be added 2g/kg/d (0.4ml/kg/h of 20% solution)

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Medication

- Carnitine: Give by continuous infusion of 4 – 8 mg/kg/hour.
- Metronidazole 7.5 mg/kg every 8 hours oral or intravenous
- Treat any infection
- Treat constipation (which increases propionate absorption from the gut. Do **not** use lactulose as this can be fermented to propionate by gut bacteria)
- If hyperammonaemic (> 200 μmol/l in first 24 hours or >250 μmol/l thereafter) consider N-carbamylglutamate 250 mg/kg as a single oral dose if available. This may be repeated. If persistent hyperammonaemia discuss with regional specialist metabolic service. Sodium benzoate 250 mg/kg/d may also be given either as a continuous infusion or enterally.

Medicines to be avoided - Sodium Valproate; Lactulose

5. Progress:

Monitoring: Reassess after 4-6 hours or earlier if there is any deterioration or no improvement Clinical assessment should include Glasgow coma score (for details click here) and blood pressure.

Blood tests: Blood pH and gases
Ammonia, Glucose (laboratory), Lactate
Urea and electrolytes,
Full blood count
Calcium, Phosphate, ALP and Amylase/lipase if pancreatitis a possibility

If improving, continue and for intravenous fluids after 6 hours please refer to the previous section

If there has been no improvement or deterioration (clinical state, acidosis, hyperammonaemia, fluid overload), seek specialist help. Haemofiltration (haemodialysis) and other treatment may need to be considered urgently. Note peritoneal dialysis is less efficient. Exchange transfusion is dangerous and should not be used.

If the patient has been unwell for sometime and not getting a vitamin supplement, consider giving a complete vitamin supplement intravenously (thiamine deficiency may be a particular problem).

6. Re-introduction of enteral feeds:
Enteral feeds with some protein should be introduced as early as possible, as this allows a much higher energy intake and reduces the risk of malnutrition. If necessary, consult your local dietitian for more details. If enteral feeds cannot be introduced within 48 hours start total parenteral nutrition (TPN) early to avoid malnutrition. (Note only moderate protein restriction when using TPN is necessary. Discuss with specialist metabolic team)

7. Going Home: Only allow the child home if you and the family are entirely happy and you have discussed the problems with the consultant on call. The family must have a clear management plan and be prepared to return if the child deteriorates.

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For further information please refer to:

Saudubray J-M, van den Berghe G, Walter JH. (editors) Inborn Metabolic Diseases. Diagnosis and treatment. 5th Edition. Springer 2012

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